

Preoperative Risk Factors for Fibrosarcomatous Transformation in Dermatofibrosarcoma Protuberans

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Abstract. *Background/Aim:* Dermatofibrosarcoma protuberans (DFSP) is a soft-tissue sarcoma with a high risk of local recurrence, though typically never metastasizes. DFSP can transform into high-grade fibrosarcoma (DFSP-FS), which has a risk of metastasis. Currently, treatment for DFSP includes Moh's micrographic surgery (MMS); however, this is not recommended for DFSP-FS. Often, the transformation to DFSP-FS is not recognized until the final histological diagnosis. At that point, wide local excision (WLE) of a previous MMS site can be morbid. As such, we analyzed patient risk factors to allow identification of DFSP-FS transformation at presentation. *Patients and Methods:* We reviewed 368 (174 female, 194 male) patients with a mean age of 42 years from two sarcoma centers. A total of 319 (87%) patients had a history of DFSP and 49 (13%) had DFSP-FS. *Results:* When comparing patients with a DFSP to those with a DFSP-FS, patients with a DFSP-FS were more likely ($p<0.05$) to be older, female and with larger tumors. A painful mass and rapidly enlarging mass were associated with DFSP-FS. *Conclusion:* Patients who presented with DFSP-FS were found to typically have a larger, painful, and growing mass. Patients with these features should be referred for WLE over MMS at presentation.

Dermatofibrosarcoma protuberans (DFSP) is the most common dermal sarcoma, characterized by slow-growing, nodular lesions with a classically infiltrative growth pattern

(1-3). DFSP is known to be locally aggressive with a risk of local recurrence ranging from 2-21%; however, patients typically do not develop metastatic disease (4). Rarely, DFSP can transform into a higher-grade malignancy with fibrosarcomatous changes (DFSP-FS), which has a higher risk of local recurrence and also a risk of metastatic spread of up to 15% (4-6).

Historically, the mainstay of treatment for DFSP has been wide local excision (WLE), with a goal to obtain a 3 cm radial margin, including the deep fascia (7). Moh's micrographic surgery (MMS) has shown promise in reducing the risk of local recurrence by allowing complete assessment of all surgical margins at the time of resection, thereby reducing the amount of tissue resected and improving margin control (8, 9). Although MMS appears favorable for the treatment of DFSP (7), the use of MMS is not indicated for patients with DFSP-FS (10). One challenging feature of DFSP-FS is its similarity to DFSP, as it is clinically indistinguishable from DFSP and often not diagnosed until after resection of the entire tumor specimen when the final pathology opinion is rendered (10). As such, DFSP-FS tumors are at high risk for inadvertent excision. Although previous series have shown no difference in recurrence risk following re-excision of soft-tissue sarcoma tumor beds (11, 12), in order to close primary MMS excision beds, Moh's surgeons often use undermining or local advancement flaps (9), potentially increasing the size of the tumor bed, which would need to be re-excised following DFSP-FS diagnosis, and also increases the size of the radiotherapy field if required as part of definitive management. To reduce the surgical morbidity that could be imparted with re-excision of DFSP-FS, identifying preoperative tumor and patient-related factors associated with DFSP *versus* DFSP-FS could allow for appropriate risk-stratification of patients

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Table I. Comparison of patient characteristics.

Preoperative characteristic	All patients (n=368)	DFSP (n=319)	DFSP-FS (n=49)	p-Value
Patient age	41±16 years	41±15 years	49±18 years	<0.01
Male gender	174 (44%)	159 (50%)	15 (33%)	0.01
Female gender	194 (56%)	160 (50%)	34 (67%)	
Truncal tumor	136 (37%)	117 (37%)	19 (39%)	0.94
Upper extremity tumor	126 (34%)	109 (34%)	17 (35%)	
Lower extremity tumor	106 (29%)	93 (29%)	13 (27%)	
Tumor size	4±3 cm	4±2 cm	6±5 cm	<0.01
Painful mass	57 (15%)	41 (13%)	16 (40%)	<0.01
Rapidly enlarging mass	75 (20%)	39 (12%)	36 (73%)	<0.01

DFSP: Dermatofibrosarcoma protuberans.

to more appropriately undergo an MMS *versus* a WLE at initial presentation. Therefore, the purpose of the current study was to evaluate clinical factors that are associated with DFSP-FS *versus* DFSP.

Patients and Methods

Following institutional ethics research board review from our respective institutions, we retrospectively analyzed 368 patients who presented to two tertiary North American sarcoma centers from 1991 to 2018 with either DFSP (n=319, 87%) or DFSP-FS (n=49, 13%). The group included 194 (53%) male and 174 (47%) female patients with a mean age of 43±16 years at the time of presentation. The tumors were located at the trunk (n=137, 37%), upper extremity (n=126, 34%), or lower extremity (n=106, 29%). In addition to a mass, common complaints at the time of presentation included a rapidly enlarging mass (n=75, 19%) and a painful mass (n=57, 15%). All patients were treated with surgical excision, with a mean tumor size at resection of 4 cm (range=5 mm - 27.5 cm). All pathologies were confirmed by musculoskeletal pathologists or dermatopathologists.

Statistical analysis. Student's *t*-tests were used to analyze continuous variables, which are reported as means±standard deviations. Categorical variables were compared with the Fisher's Exact test and odds ratios (OR). All tests were two-sided. *p*-Values <0.05 were considered statistically significant.

Results

When comparing patients with a DFSP to those with a DFSP-FS, patients with a DFSP-FS were more likely to be older (49±18 *vs.* 41±15 years, *p*<0.01), female (n=34, 67% *vs.* n=160, 50%, *p*=0.01) and with larger tumors (6±5 *vs.* 4±2 cm, *p*<0.01) compared to patients with DFSP (Table I). There was no difference in the location of the tumor when comparing a DFSP *versus* a DFSP-FS (*p*=0.94). A history of painful mass (OR=3.28 95%CI=1.66-6.49, *p*<0.01) and a rapidly enlarging mass (OR=19.9, 95%CI=9.70-40.7, *p*<0.01) were strongly associated with DFSP-FS.

Discussion

DFSP is a common dermal sarcoma, which historically has been treated with WLE. Moh's micrographic surgery has become a viable treatment option for patients with DFSP, however this form of treatment is not appropriate for patients with a DFSP that has transformed into a higher-grade sarcoma (*i.e.*, DFSP-FS). As such, appropriate stratification of patients at the time of initial presentation is essential to avoid subsequent morbidity associated with the need for re-excision of an inadequately resected DFSP-FS tumor bed following initial Moh's excision. The results of the current study identify patient-related factors, which could be associated with patients presenting with DFSP-FS, and as such these patients should be referred at the time of diagnosis for WLE as opposed to MMS.

Previous series have identified fibrosarcomatous changes in patients with DFSP in 10-20% of patients (13-16), which is similar to the results of the current study (13%). There has been discrepancy noted when trying to identify factors associated with DFSP-FS compared to DFSP with respect to patient age and sex. However, compared to these previous studies (13-16), we found a strong association between age and sex, as older and female patients were more likely to present with DFSP-FS. We noted that patients with a rapidly enlarging mass, a mass >4 cm, and a painful mass were also more likely to have fibrosarcomatous changes. It was previously shown that patients with soft tissue masses presenting with rapid growth, pain, and larger size are more likely to be diagnosed with a soft-tissue sarcoma (17). In a series by Nandra *et al.* (17), the authors noted that if a patient presented with a large (>4 cm), painful, and enlarging mass, their risk of having a sarcoma was over 60%.

Although DFSP is considered a tumor with potential for local recurrence, it has a very low risk of metastatic disease (4, 10). Unlike DFSP, DFSP-FS harbors true malignant potential due to its increased risk of local recurrence, metastatic disease, and death due to disease compared to patients with DFSP (4, 10). For patients who present with DFSP, MMS is a reasonable

treatment option; however, patients with DFSP-FS should be referred for WLE, since patients undergoing a WLE with ≥ 2 cm margin have the lowest risk of tumor recurrence (10, 18-21). In addition, MMS often involves an initial debulking of the mass followed by removing areas of positive margins in layers to finally achieve a negative margin (22, 23). Although the final resections are ultimately negative, this would still be considered a contaminated or intralesional type of resection, which has been shown to potentially increase the risk of local recurrence (24, 25), which could impart an increased risk of death due to disease recurrence (26). Thus, in patients where there is concern for transformation of DFSP into DFSP-FS, they should be referred to a sarcoma specialist for WLE with a negative surgical margin.

Our study is not without limitations. We were limited to the data we can gather from the medical record, therefore different presenting characteristics, which were not captured in the records, may be associated with DFSP-FS. The retrospective nature of the study limits the analyses we can perform. This study was undertaken at two large tertiary oncology centers in North America, and as such there is bias in our patient population and these conclusions may not be generalizable to other centers. Since the purpose of this study was to identify factors present at initial tumor presentation that could suggest a DFSP-FS, we did not examine the results of treatment outcome and oncologic follow-up.

The results of the current series revealed that DFSP-FS was more common in older and female patients. There should be a clinical suspicion for DFSP-FS compared to DFSP when patients present with a large, painful tumor that is recently growing. These patients should be referred to a sarcoma center for evaluation and biopsy, with a plan for WLE.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Mallett: Drafting of initial and final manuscript, data collection, data analysis; Almubarak: Data collection, data analysis; Claxton: Data collection, data analysis; Ferguson: Review and editing of final manuscript; Griffin: Review and editing of final manuscript, data collection; Rose: Review and editing of final manuscript; Wunder: Review and editing of final manuscript, supervision; Houdek: Drafting of initial and final manuscript, data analysis, supervision.

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